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# Combining Antiplatelet and Anticoagulant Therapies

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**Antiplatelet therapy** is the cornerstone for both primary and secondary prevention therapies for ischemic events resulting from coronary atherosclerotic disease. Dual antiplatelet therapy (aspirin plus a thienopyridine, usually clopidogrel) has assumed a central role in the treatment of acute coronary syndromes and after coronary stent deployment. In addition to antiplatelet therapy, anticoagulant therapy might be indicated for stroke prevention in a variety of conditions that include atrial fibrillation, profound left ventricular dysfunction, and after mechanical prosthetic heart valve replacement. For this reason, the use of triple antithrombotic therapy (a dual antiplatelet regimen plus warfarin) is expected to become more prominent, given an aging patient population. But although triple therapy can prevent both thromboembolism and stent thrombosis, it is also associated with significant bleeding hazards. Furthermore, when bleeding events do occur, the challenge of balancing the risk of stent thrombosis or stroke and the need for hemostasis requires considerable expertise. It is both prudent and timely to review treatment strategies that employ combinations of antiplatelet and anticoagulant therapies as well as strategies aimed at reducing bleeding risk in patients treated with these therapies.

Evidence-based medicine serves as the cornerstone for implementing and refining optimal strategies of care. But as the number and complexity of therapies increase in the context of an aging patient population (with an attendant admixture of coexistent diseases), the potential for significant adverse interactions grows. This is of particular concern in the setting of

cardiovascular and cerebrovascular diseases, where the combination of antiplatelet and anticoagulant therapies is an increasingly ubiquitous consideration. It is therefore appropriate that we now review this issue, focusing specifically on risks as well as means for optimizing outcomes in the setting of combined antiplatelet and anticoagulant therapy.

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Background

Antiplatelet Therapy for  
Coronary Atherosclerotic Disease

Antiplatelet therapy is widely used for secondary prevention of ischemic events associated with established coronary atherosclerotic disease (CAD) (1). In the Antithrombotic Trialists Collaboration Group meta-analysis, which examined 287 studies (comprising 135,000 patients) and compared antiplatelet therapy versus control in high-risk patients (2), antiplatelet therapy was shown to reduce the occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or vascular death. In patients with acute MI, the immediate administration of aspirin (ASA) has been shown since the 1980s to lower the rate of periprocedural MI and subsequently has become both a quality-of-care metric and a Class I indication in practice guidelines (American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions [ACC/AHA/SCAI] as well as the European Society of Cardiology [ESC]), as outlined in Table 1 (3–5). These guidelines recommend prolonged dual antiplatelet therapy for at least 12 months after placement of drug-eluting stents (DES).

The optimal dose of ASA for acute and long-term treatment is less well-established. Aspirin-dosing regimen has important implications for bleeding, particularly in patients receiving “triple therapy” (2 antiplatelet agents plus warfarin). A wide range of doses has been evaluated, from 75 mg/day to as high as 1,500 mg/day (1,2). It has been suggested that a dose of 75 to 162 mg/day might be more effective than higher doses, on the basis of potentially adverse effects of higher doses on the production of the vasodilator prostacyclin (PGI<sub>2</sub>). In the Antithrombotic Trialists’ Collaboration (2), no statistically significant dif-

ferences in clinical outcomes were observed between trials that directly compared doses of ASA <75 mg/day versus ≥75 mg/day. With a random effects model assessing the effects of ASA on mortality at 30 days, the odds ratio (OR) for the overall population was 0.82 (95% confidence interval [CI]: 0.71 to 0.96). Among post-infarction patients, the OR was 0.86 (95% CI: 0.73 to 1.00), whereas among patients with unstable angina the OR was 0.61 (95% CI: 0.40 to 0.94). However, as the authors point out, doses <75 mg have been less widely studied than doses of 75 to 150 mg. In general, higher ASA doses are associated with increased bleeding. The optimal ASA dose regimens required for primary versus secondary prevention or for stable versus unstable coronary syndromes remain controversial.

Kong et al. (6) evaluated the optimal dose of ASA in the setting of acute coronary syndrome (ACS) in a meta-analysis of trials with ASA doses ranging from 300 mgm to 1.5 mg/day. With a variety of modeling techniques to adjust for differences in patient and temporal characteristics, they found that when the effects of an ASA dose were considered, the odds of death or MI increased 1.14-fold for each doubling of the dose, suggesting “that higher doses of aspirin produced less benefit after adjusting for temporal trends” (6).

Recently, results from the retrospective observational BRAVO (Blockade of the IIb/IIIa Receptor to Avoid Vascular Occlusion) trial were used to evaluate the relationship between prescribed ASA dose (<162 mg/day vs. ≥162 mg/day) and clinical outcomes in 4,589 patients who presented with a variety of acute ischemic syndromes (unstable angina [UA] or MI within 14 days, transient ischemic attack within 30 days, stroke within 5 to 30 days) or who had clinical involvement of 2 vascular beds with atherosclerosis (7). Clinical outcomes were analyzed to 366

Table 1

ACC/AHA/SCAI and ESC Recommendations for Aspirin Administration

Timing	Society Recommendations	
	ACC/AHA/SCAI	ESC
Before PCI	Patients already taking daily long-term aspirin should take 75 to 325 mg of aspirin before PCI is performed (Class I, LOE: A)	
	Patients not already taking long-term aspirin should be given 300 to 325 mg of aspirin at least 2 h and preferably 24 h before PCI (Class I, LOE: C)	Patients not already taking daily aspirin should be given a loading dose of 500 mg orally >3 h before procedure or 300 mg intravenously directly before the procedure (Class I, LOE: B)
After PCI	If a bare-metal stent has been placed, aspirin 162 to 325 mg daily should be given for at least 1 month, and then daily long-term aspirin should be continued indefinitely at doses of 75 to 162 mg (Class I, LOE: B)	For chronic use, there is no need for doses higher than 100 mg daily (Class I, LOE: B)

Data from Antman et al. (3), King et al. (4), and Silber et al. (5).

ACC/AHA/SCAI = American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions; ESC = European Society of Cardiology; LOE = level of evidence; PCI = percutaneous coronary intervention.

days. In a multivariable Cox proportional hazards model, higher doses of ASA predicted both lower all-cause mortality as well as an elevated risk of bleeding (15.3% vs. 11.2%,  $p < 0.0001$ ). Higher-dose ASA was not associated with a significant difference in the composite end point of death, nonfatal MI, or nonfatal stroke (6.1% vs. 6.2%,  $p = 0.74$ ) when compared with lower doses.

The major hazard of ASA is bleeding (1,2,6–10). The Antithrombotic Trialists' Collaboration (2) identified a proportional increased risk of major extracranial bleeding with antiplatelet therapy (OR: 1.6, 95% CI: 1.4 to 1.8), but only the excess of nonfatal bleeding was significant. Other studies have demonstrated that ASA doses of  $\geq 325$  mg/day are associated with a  $>2$ -fold increase in gastrointestinal (GI) bleeding events compared with doses  $< 325$  mg (8). In a pooled analysis of 55 randomized controlled trials (RCTs) (9), 75,005 patients were treated with low-dose ASA versus placebo. Among patients given placebo, the weighted incidence of any major bleeding was 0.18%/year, and the absolute rate increase with ASA above placebo was 0.13%/year. The weighted incidence of major GI bleeding with placebo was 0.12%/year, and the absolute rate of increase with ASA above placebo was 0.12%/year. Finally, among placebo-treated patients, the weighted incidence of any intracranial bleeding was 0.05%/year, and the absolute rate increase with ASA above placebo was 0.03%/year. Thus, compared with placebo, treatment with open-label ASA increased the risk of major bleeding (relative risk [RR]: 1.71; 95% CI: 1.41 to 2.08), major GI bleeding (RR: 2.07, 95% CI: 1.61 to 2.66), and intracranial bleeding (RR 1.65; 95% CI: 1.12 to 2.44). Despite randomization for baseline patient characteristics, there might be unmeasured differences, and some of the patients—particularly older patients—might have a heightened risk of bleeding. Nevertheless, in patients at high risk for cardiovascular ischemic events, the relative benefit of ASA outweighs the risk of bleeding, particularly when lower doses are prescribed. Unlike the benefit for anti-ischemic effects, the risk of ASA-associated bleeding, particularly in the GI tract, seems to be dose-dependent. A nonrandomized observation from the BRAVO trial of lotrafiban indicates that, when patients treated with doses of 75 to 162 mg/day were compared with those receiving doses  $> 162$  mg, the risk of serious bleeding was lower (2.4% vs. 3.3%), as was the likelihood of transfusion (1.0% vs. 2.0%, respectively) (11). Findings were concordant in a more recent observational analysis of patients undergoing percutaneous coronary intervention (PCI) within the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial for ACS. Patients were stratified according to ASA dose (75 to 100, 125 to 175, or  $> 200$  mg/day). There was no evidence of difference in any of

the ischemic composites according to dose, whereas the adjusted risk of bleeding was lower among patients treated with the lower doses compared with the higher doses (hazard ratio [HR]: 2.03, 95% CI: 1.15 to 3.57). There also seemed to be an interaction with clopidogrel treatment; among patients in the lower 2 dose ranges, the risk of bleeding did not increase after treatment with clopidogrel, whereas among patients receiving the higher dose, it did (3.3% for ASA alone, 4.5% for ASA with clopidogrel; HR: 1.39, 95% CI: 0.75 to 2.57) (12).

## Dual Antiplatelet Therapy

Bleeding risks have become more problematic with the advent of widespread and prolonged therapy with the combination of ASA and a thienopyridine (typically clopidogrel) (1,9,13). Combination antiplatelet therapy with the novel third-generation thienopyridine prasugrel plus ASA was associated with an increased risk of Thrombolysis In Myocardial Infarction major noncoronary bypass surgery-related bleeding events when compared with ASA plus clopidogrel combination (2.4% and 1.8%, respectively;  $p = 0.03$ ) (14). Dual antiplatelet therapy provides incremental platelet inhibition (compared with either agent alone) and more effective suppression of adverse ischemic events and has been studied in the settings of medical therapy and PCI as well as in stroke prevention and treatment.

The 2007 ACC/AHA clinical practice guidelines (15) for the care of patients with UA/non-ST-segment elevation myocardial infarction give a Class I indication for ASA to be given immediately and continued indefinitely and for clopidogrel to be administered and continued for at least 1 month and preferably for up to 1 year after the index event, regardless of whether a conservative or invasive treatment strategy was initially selected. In patients in whom angiography is performed and obstructive coronary disease is identified but who do not have revascularization, an oral loading dose of clopidogrel (300 to 600 mg) should be administered, followed by 75 mg/day for at least 1 year. A 300-mg clopidogrel loading dose should be given the day before elective PCI to achieve effective platelet inhibition, whereas a 600-mg clopidogrel regimen should be used if more rapid antiplatelet effect is needed (16).

Recommendations regarding duration of clopidogrel therapy after ACS are based on observations from multiple RCTs, including the CURE trial, which enrolled 12,562 subjects with UA or non-ST-segment elevation myocardial infarction (17). In CURE, subjects were randomly assigned to receive either clopidogrel (300-mg oral loading dose, followed by 75 mg/day) in combination with ASA or ASA alone. Dual therapy was associated with a 20% RR reduction in the primary composite end point (MI, stroke, or cardiovascular death) to 1 year of follow-up (from 11.4% to

9.3%), findings that support early clopidogrel administration in patients managed with medical therapy, because the ischemic event curves diverge early in favor of clopidogrel. However, dual therapy was also associated with an excess in major bleeding events (3.7% vs. 2.7%;  $p = 0.003$ ). Similarly, in the post-randomization but pre-specified analysis of the CURE trial involving patients who underwent PCI (PCI-CURE) (18), a 31% RR reduction in the composite occurrence of cardiovascular death or MI at 1 year was observed: from 12.6% in subjects treated with ASA alone to 8.8% in subjects receiving dual therapy. The CREDO (Clopidogrel for Recurrent Events During Observation) trial evaluated outcomes in 2,116 patients after PCI. At 1 year, long-term dual antiplatelet therapy with clopidogrel was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke (95% CI: 3.9% to 44.4%,  $p = 0.02$ ) versus ASA alone. (19). Although data from the COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) and CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) trials extend only to 30 days, the parallel but longer-term findings of the CURE, CREDO, and the subgroup with prior MI or stroke within the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial provide evidence that clopidogrel's effect is durable.

Conversely, it is important to remember that both the presence and degree of benefit associated with dual antiplatelet therapy are likely to depend on characteristics of the specific patient cohort. For example, the CHARISMA trial studied a population at risk for thrombotic complications of atherosclerosis but at a lower risk than patients in the CURE or CREDO trials. Although dual antiplatelet therapy (ASA plus clopidogrel) was not more effective than ASA alone in the primary prevention cohort of the CHARISMA trial (patients with high risk profile but no established atherothrombotic disease), dual therapy was more effective in those patients with clinically evident cardiovascular disease at study entry (secondary prevention cohort) (20); at a mean follow-up of 27.6 months, the rate of cardiovascular death, MI, or stroke in this secondary prevention cohort was significantly lower (6.9% vs. 7.9%,  $p = 0.046$ ) among patients assigned to dual therapy compared with ASA alone. However, moderate bleeding events were increased to 2% with dual therapy compared with 1.3% with ASA only (HR: 1.60, 95% CI: 1.16 to 2.20,  $p = 0.004$ ).

Studies of dual therapy have demonstrated a variable but overall increased frequency of bleeding events, possibly influenced by both duration of therapy as well as ASA dosage. In a meta-analysis of 22 trials, ASA alone increased the risk of major bleeding compared with placebo (RR: 1.71, 95% CI: 1.41 to 2.08) (9). Although not all trials have

yielded concordant results, in general, lower doses of ASA ( $<100$  mg) are associated with similar anti-ischemic efficacy but reduced bleeding event rates when given in combination with clopidogrel. Pooled analyses of multiple trials have demonstrated a rough but direct relationship between ASA dose and major and/or minor bleeding events, whereas no additional anti-ischemic efficacy has been seen with higher doses; however, these data are limited by substantial differences in reporting of complications. The optimal dose of ASA to be used in combination with a thienopyridine would seem to be  $\leq 100$  mg (5,13,21,22).

### Dual Antiplatelet Therapy and Coronary Stenting

Coronary stenting disrupts the endothelial lining and triggers thrombin production, with subsequent deposition of platelets and mural thrombi at the site of endoluminal injury. Multiple RCTs (23) have compared different adjunctive pharmacotherapy regimens in subjects receiving bare-metal stents (BMS) (Table 2); study results have been concordant (24–28) and form the basis of the ACC/AHA recommendations for dual antiplatelet therapy.

The optimal duration of clopidogrel therapy after deployment of BMS has been controversial. Whereas an abbreviated regimen of 2 weeks has been suggested, longer treatment ( $\geq 6$  months) has been shown to provide benefits that, although possibly unrelated to the stented site, might reflect a salutary effect of systemic treatment for a systemic disease process (reduction in incidence of death, MI, or stroke) (19,29,30). There has also been recent recognition that both late (30 days to 1 year) and very late ( $>1$  year) thrombosis might complicate the use of BMS, particularly when deployed for more complex (“off-label”) scenarios (18,31,32). Thus, in patients treated medically after presentation for ACS as well as those treated after PCI (BMS or DES), extended-duration dual therapy has demonstrated benefits, and care guidelines have correspondingly recommended progressively longer treatment durations. However, the balance of reduction in thrombotic complications versus risk of increased bleeding events in these patients remains poorly defined.

Late thrombosis after DES implantation has catalyzed intense interest in defining an optimal duration of dual therapy, thereby prompting a re-examination of the pathophysiologic mechanisms responsible for recurrent ischemic events after revascularization. Data from RCTs and registries were analyzed to formulate an AHA/ACC/SCAI/American Cancer Society/American Diabetes Association Science Advisory (23), which recommends extending dual antiplatelet therapy for at least 12 months after DES deployment and cautions that premature discontinuation might be associated with stent thrombosis and a consequent



**Table 2**

## After Bare-Metal Stent Placement, ASA Plus Thienopyridine Reduces Cardiac Events Compared With ASA Alone or With Oral Antithrombins

Study (Ref. #)	Patients Studied, n	Patients Treated, n	MACE, %*			p Value
			ASA + Thienopyridine	ASA + Warfarin	ASA Only	
ISAR (24)	517	626	1.6	6.2	—	0.01
FANTASTIC (25)	473	485	5.7†	8.6†	—	0.37
STARS (26)	1,653	1,965	0.5	2.7	3.6	0.0001
MATTIS (27)	350	350	5.6	11.0	—	0.07
Hall et al. (28)	226	358	0.8	—	3.9	0.1

\*Cardiac death, acute myocardial infarction, or repeat target vessel revascularization at 30 days (except for the FANTASTIC [Full Anticoagulation Versus Aspirin and Ticlopidine] study). †Death, myocardial infarction, or stent occlusion at 6 weeks.

ASA = aspirin; ISAR = Intracoronary Stenting and Angiographic Results; MACE = major adverse cardiovascular events; MATTIS = Multicenter Aspirin and Ticlopidine Trial After Coronary Stenting; STARS = Stent Anti-thrombotic Regimen Study.

risk for death and/or nonfatal Q-wave MI. The Advisory recommends deferral of elective surgical procedures for at least 1 year to accommodate dual antiplatelet therapy.

Studies comparing DES and BMS have shown that the timing of stent thrombosis might differ (33–39). Stent thrombosis tends to occur earlier in BMS, whereas stent thrombosis in DES seems to trend later. Of particular concern is the observation that DES thrombosis might continue to occur (albeit at a very low rate) over time (40). In an attempt to prevent late thrombosis, a longer (possibly indefinite) duration of dual therapy is frequently recommended, especially after DES in the setting of documented severe extensive atherosclerotic disease.

These recommendations have important implications for the subsequent performance of surgical procedures that require stopping antiplatelet therapy, which can lead to stent thrombosis. Conversely, extended dual therapy prolongs the “window of vulnerability” for bleeding, particularly in scenarios where concomitant warfarin might be necessary.

## Anticoagulant Therapy

Warfarin monotherapy has been the mainstay of treatment for patients with atrial fibrillation (AF), prosthetic heart valves, markedly reduced left ventricular function or left ventricular thrombus, as well as for prevention or treatment of deep venous thrombosis and pulmonary embolism. Randomized clinical trials have shown that warfarin is superior to either ASA or clopidogrel for prevention of stroke in patients with AF, and observational data seem to have established it as the standard antithrombotic treatment in patients with mechanical valve prostheses. Although warfarin is currently indispensable in these settings, the combination of ASA and a thienopyridine is similarly indispensable after stent implantation, and several random-

ized clinical trials have shown the superiority of this combination in patients who receive stents. A major clinical issue that is currently unresolved centers around the management of patients who have a firm indication for warfarin therapy and who have received stents and thus also have an indication for dual antiplatelet therapy. This question is particularly vexing among patients who have received DES and who, with the indication for long-term treatment with dual antiplatelet therapy, have both a need for as well as prolonged exposure to the risk of triple therapy. Unfortunately, there are very limited data to provide guidance in this arena, and the only randomized trials that offer any solace to the perplexed clinician have compared combined warfarin and ASA with either warfarin or ASA.

Warfarin has also been evaluated in patients with recent MI treated with warfarin versus placebo (but no ASA) (41). In this trial, there was a reduction in risk of mortality of 24% (95% CI: 4% to 44%,  $p = 0.027$ ). The combined incidence of major bleeding, however, was 0.6%/year. In the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial (42), oral anticoagulant therapy alone after MI was associated with a 1.4% annual incidence of major bleeding versus 0.4%/year with placebo and with a significant 53% and 40% RR reduction of reinfarction (annual incidence 2.3% vs. 5.1%) and cerebrovascular events (annual incidence 0.7% vs. 1.2%) compared with placebo, respectively. Combination therapy of warfarin and low-dose ASA has also been evaluated in patients with ACS, mainly in survivors of acute MI. In the WARIS II (Warfarin–Aspirin Reinfarction Study) (43), APRICOT 2 (Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis 2) (44), and ASPECT-2 (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) (45) trials, warfarin administered with an international normalized ratio (INR) goal of 2.0

to 2.5 in combination with low-dose ASA, compared with ASA alone, was effective in reducing adverse ischemic events, including the composite occurrence of death or nonfatal reinfarction, as well as recurrent coronary occlusion after ST-segment elevation myocardial infarction. However, these trials also identified an increased risk of bleeding associated with combination antiplatelet-anticoagulant therapy; in the WARIS-II trial, for example, 28 of 69 nonfatal major bleeding episodes occurred in patients taking both warfarin and ASA compared with 33 of 69 in patients taking only warfarin and 8 in patients taking only ASA (43).

Indeed, combining warfarin with even a single antiplatelet agent makes bleeding a more prominent concern. The Warfarin Antiplatelet Vascular Evaluation Trial investigators randomly assigned 2,161 patients with peripheral arterial disease to receive either a single antiplatelet agent (choice of agent at physician's discretion) in combination with warfarin (target INR 2.0 to 3.0), or antiplatelet therapy alone (46). At a mean follow-up of 35 months, combination (warfarin plus antiplatelet) therapy was associated with frequent occurrence of fatal (0.9% vs. 0.3%), life-threatening (4.0% vs. 1.2%), intracranial (1.3% vs. 0%), and moderate (2.9% vs. 1%) bleeding events as well as with a more than 3-fold higher incidence of the composite end point, which included life-threatening or moderate bleeding (6.9% vs. 2.2%). Importantly, this trial defined moderate bleeding as intraocular hemorrhage or bleeding requiring transfusion of 1 to 3 U of blood products, whereas life-threatening bleeding was defined as either fatal, intracranial requiring surgical intervention, or transfusion requiring  $\geq 4$  U of blood products. Finally, combination therapy (vs. antiplatelet therapy alone) did not significantly affect the incidence of the composite ischemic end point (cardiovascular death, MI, or stroke) that was observed in 12.2% and 13.3% of patients, respectively (RR: 0.92; 95% CI: 0.73 to 1.16;  $p = 0.48$ ).

Testa et al. (47) used an adjusted indirect meta-analysis to study the clinical outcome of combination therapy with ASA plus warfarin versus ASA alone. They identified 10 studies that included 7,836 patients. In this group, Testa et al. (47) demonstrated a significant 27% RR reduction of major adverse events (death, MI, thromboembolic stroke) in the combination group but a more than 2-fold increase in incidence of major bleeding events.

Bleeding risk with warfarin therapy has been the subject of intense interest in preventing stroke in patients with AF (48). The incidence of AF increases with age and greatly increases the risk of stroke. For patients with AF, warfarin therapy has proven superior for stroke prevention, compared with either ASA alone or dual antiplatelet therapy (49). However, the risk of bleeding with warfarin raises substantial concerns, particularly in

older patients at risk for both bleeding as well as stroke due to AF. In a series of such patients  $\geq 65$  years of age, a major hemorrhagic event occurred in 7% during their first year of warfarin treatment (50).

Unfortunately, there is very limited information regarding patients treated with triple therapy, who present significant clinical challenges because of the imperative to balance bleeding risks against risks entailed in stopping 1 of the 3 therapies. Discontinuation of warfarin might increase the potential for stroke, whereas discontinuation of clopidogrel might result in increased risk for stent thrombosis; both events are associated with significant morbidity and mortality. Most available data have been derived from single-center registries or small case-controlled series or, in a few cases, from post hoc analyses of prospective studies. Most of these studies focused on the risk of bleeding rather than the rate of MI or stent thrombosis. Antithrombotic strategies adopted in patients who require oral anticoagulation as well as antiplatelet therapy can vary and are often left to the judgment of the attending physician. In fact, indications briefly reported on this topic by guidelines of the international cardiovascular societies have a Class IIb recommendation and a Level of Evidence: C (3-5). In published studies, the frequency and severity of bleeding events vary substantially, possibly due to differences in bleeding definition, sample size, intensity of anticoagulant regimen, ASA dose, and the clinical characteristics of the respective patient populations. Furthermore, in several of these reports, it has proven difficult to discriminate patients who actually received triple therapy from those who received only a single antiplatelet agent plus warfarin.

In a study of 21,443 elderly patients after acute MI, Buresly et al. (51) evaluated bleeding complications associated with combination therapies including ASA, thienopyridine derivatives, and warfarin. Patients receiving ASA and warfarin were at modest risk for bleeding (0.08/patient-year) compared with patients receiving ASA alone (0.03/patient-year). A trend toward increased risk of intracranial bleeding was observed in patients treated with ASA and warfarin, compared with ASA alone (11.1% vs. 6.4%,  $p = 0.14$ ). Only 141 subjects received triple therapy with ASA, a thienopyridine, and warfarin; just 1 bleeding event was observed among these patients. The small number of subjects and events in the triple therapy group precluded calculation of an HR.

In a small retrospective study of triple therapy ( $n = 66$ ) from the Mayo Clinic PCI database for procedures performed from 2000 to 2002, no patients died or had stent thrombosis, but 6 patients (9.2%) had a bleeding event (52). Of these, only 2 required transfusion, and there was no intracranial bleeding. Thus, although the risk of bleeding

was increased, the bleeding events did not have major clinical consequences. Of note, all bleeding events occurred in patients with nonoptimal control of INR or pre-existing GI lesions, emphasizing the importance of bleeding risk stratification and careful INR monitoring.

Similarly, Khurram et al. (53) observed increased bleeding with triple therapy after coronary stenting in 107 patients with a mean follow-up of 211 days. Of note, 70% of these patients had AF and 75% received a DES. Major bleeding was defined as bleeding that was significantly disabling, intraocular, or required  $>2$  U of blood products; minor bleeding was defined as other bleeding events that led to interruption of antiplatelet or anticoagulant therapy. Patients receiving triple therapy had more major bleeding (6.6% vs. 0%,  $p = 0.014$ ) and more minor bleeding (14.9% vs. 3.8%,  $p = 0.01$ ) compared with a control group of patients who received dual antiplatelet therapy. Major bleeding complications in patients receiving triple therapy occurred 2 to 10 months after intervention. After adjusting for confounding variables through multivariate analysis, triple therapy was an independent predictor of bleeding, with an HR of 5.44 ( $p = 0.001$ ).

Mattichak et al. (54) evaluated 40 patients who underwent stent placement for acute MI and were treated with triple therapy. This group was compared with 42 patients who received stents for acute MI but were treated with dual antiplatelet therapy. Significant differences in baseline characteristics between the groups were observed: patients treated with warfarin were older, had a higher frequency of prior MI, and had a higher baseline creatinine. At 12 months of follow-up, patients receiving triple therapy showed a trend toward higher rates of GI bleeding (15% vs. 9%,  $p = 0.12$ ) and more transfusions (21% vs. 3.5%,  $p = 0.026$ ).

More recently, Porter et al. (55) evaluated 180 patients who received PCI for an emergent or urgent indication and were subsequently treated with triple therapy. Although the duration of therapy was only 30 days, 20 patients developed bleeding complications. In 18 of those patients, bleeding was minor (defined as hematocrit decrease of  $<10\%$  if clinical bleeding was observed or of 10% to 15% if no clinical bleeding was detected), and there were no intracranial bleeds. Two patients developed major femoral access-site hematomas related to the catheterization procedure itself. After 30 days, 104 patients continued treatment with only warfarin and ASA; although the ASA dose administered in this study was 100 mg/day, 19 patients had bleeding events (18 minor) and no intracranial bleeding was observed.

Nguyen et al. (56) evaluated 580 patients who underwent stenting for ACS and were discharged on warfarin plus dual antiplatelet therapy as part of the GRACE (Global Registry

of Acute Coronary Events) registry. At 6 months, a significant reduction in stroke was observed in patients receiving warfarin plus dual antiplatelet therapy (0.7% vs. 3.4%,  $p = 0.02$ ). No differences in major bleeding events were observed in-hospital between patients receiving warfarin plus dual therapy (5.9%) or those treated with warfarin and a single antiplatelet agent (4.6%) ( $p = 0.46$ ). No follow-up data on bleeding events were presented. In the subset of patients who received a DES ( $n = 100$ ), there were no differences between treatment regimens in the hard end points of death, stroke, unscheduled PCI, or MI at 6 months. However, patients receiving warfarin with single antiplatelet therapy had an absolute increased risk for bleeding of 2.7% during follow-up, but the total number of events was small and did not allow definitive conclusions to be drawn.

A case-control study of 239 Finnish patients receiving warfarin and undergoing PCI from 2003 to 2004 (57) evaluated a primary end point of death, MI, target vessel revascularization, or stent thrombosis and a secondary end point of major bleeding and stroke to 12 months of follow-up. The most frequent indication for warfarin therapy was presence of AF, and triple therapy was used in 106 patients (48.4%). Stent thrombosis was observed more frequently (15.2%) among patients receiving warfarin plus ASA, compared with those receiving triple therapy (1.9%), whereas stroke was more frequent in patients treated with dual antiplatelet therapy only (8.8% vs. 2.8% with triple therapy). Major bleeding (defined as hemoglobin decrease of  $\geq 4.0$  g/dl, transfusion of  $\geq 2$  U of blood products, need for corrective surgery, or intracranial or retroperitoneal hemorrhage) was similar between groups (6.6% triple therapy; 6.1% warfarin plus ASA; 11.1% warfarin plus clopidogrel; and 11.8% ASA plus clopidogrel). Compared with an age- and sex-matched control group, patients receiving warfarin had a worse baseline cardiovascular risk profile, and therapy with warfarin (combined with single or dual antiplatelet agents) was an independent predictor of both major bleeding (8.2% warfarin vs. 2.6% no warfarin; OR: 3.3, 95% CI: 1.3 to 8.6;  $p = 0.014$ ) and cardiac events (death, MI, target vessel revascularization, stent thrombosis) at 1 year (21.9% warfarin vs. 11.0% no warfarin; OR: 1.7, 95% CI: 1.0 to 3.0,  $p = 0.05$ ). Cardiac events were in large part due to the higher incidence of stent thrombosis in the warfarin plus ASA group.

Further observational data (58) from a series of 127 patients receiving warfarin (59% of whom had AF) who were treated with coronary stents and discharged on triple therapy demonstrate a 7.1% total bleeding incidence (4.7% major) during 21-month follow-up. Of note, major bleeding events were fatal in 3 (50%) cases and were intracranial

in 4 (approximately 66%) patients. These frequencies should, of course, be interpreted cautiously in light of the small number of events.

In a recent series of 426 patients with AF who received stents, a variety of pharmacological strategies were evaluated, with triple therapy being administered to 213 (50%) patients (59). Adverse events were frequent (35%) in this cohort, with major bleeding reported in 12.3% of patients; all-cause mortality was also high at 22.6%. Interruption of warfarin therapy after intervention was associated with an increased risk of cardiovascular events at a mean of 595 days (HR: 4.9, 95% CI: 2.17 to 11.09;  $p < 0.01$ ) and was largely driven by thromboembolic complications. The clinical benefit of continuing warfarin outweighed a 66% relative increase in risk of major bleeding. In patients receiving DES (40% of the study population), there was no significant difference in the incidence of major adverse cardiac events by multivariate analysis, although such patients had a slightly higher rate of stent thrombosis (overall incidence, however, remained low). Unfortunately, no information on bleeding was provided for the DES cohort.

In aggregate, these studies illustrate the complex issues facing those who attempt to formulate strategies for care of patients treated with warfarin who also require dual antiplatelet therapy. As noted in the preceding text, the most common clinical scenario for such patients is AF with coexistent CAD requiring a stent; patients with mechanical prosthetic heart valves and concomitant CAD who require a stent comprise another important group. Some patients with deep venous thrombosis also require long-term anticoagulation, but in many patients, a duration of 3 to 6 months will suffice. Approximately 45% of patients enrolled into these studies had ACS, DES were deployed in approximately 37%, and glycoprotein IIb/IIIa inhibitors were used in fewer than 40%. Indeed, use of glycoprotein IIb/IIIa inhibitors might contribute to short-term bleeding risk after PCI. The percentage of patients who undergo stenting and require concomitant long-term oral anticoagulation is likely to increase because of the increasing number of PCI procedures and the advancing age of PCI patients (with an accompanying higher prevalence of related comorbidities). In patients who require long-term oral anticoagulation, serious consideration should be given to the use of BMS prostheses for which dual antiplatelet treatment is recommended for a shorter time after deployment.

Interpretation of data from published series is complicated by the variability in treatment strategies, including medication doses and duration of therapy, as well as variation in definitions used for bleeding events. Given the increased frequency of AF among older patients and increasingly widespread use of DES (for which dual antiplate-

let therapy is recommended for at least 1 year), the issues surrounding triple therapy will likely become even more important. Considering the prevalence of AF, thought should be given to approaches that could help avoid the need for long-term warfarin, such as left atrial appendage occlusion devices or pulmonary vein ablation. Left atrial appendage occlusion devices offer the potential to discontinue warfarin without increasing stroke risk and might eliminate the need for triple therapy in these patients (60). In an initial experience of 66 patients with AF at increased risk for stroke, warfarin could be discontinued in 90% of patients; during follow-up of  $740 \pm 341$  days, there were no strokes and only 2 transient ischemic attacks despite the discontinuation of warfarin.

The principal concern associated with triple therapy is risk of bleeding or transfusion. The frequency of such events in reported series varies, with up to 21% of patients needing a transfusion; bleeding events typically involve the GI tract. This frequency might increase with longer durations of triple therapy, which directly correlate with bleeding risk and might influence mortality in follow-up after PCI. In particular, the RR of major bleeding in patients receiving triple therapy is 3- to 5-fold higher than that observed in patients receiving dual antiplatelet therapy alone. The increase in bleeding events is confounded by the fact that patients receiving triple therapy are typically older and have multiple comorbidities, which might increase bleeding potential. Moreover, limited use of triple therapy (for 1 month) is associated with at least a 2-fold lower risk of major bleeding compared with prolonged use ( $>6$  months).

From these studies, it also seems that patients receiving dual antiplatelet therapy only after PCI (prolonged warfarin interruption) have a 3-fold increase in incidence of stroke or thromboembolic events, compared with patients receiving triple therapy or warfarin plus a single antiplatelet agent. Furthermore, there are wide differences in the reported incidence of cardiac events during follow-up, probably due to variation in antithrombotic regimens as well as in clinical risk profiles, end point definitions, and length of follow-up. However, triple therapy was associated with a lower risk of stent thrombosis and MI during follow-up; indeed, MI during follow-up might also result from stent thrombosis, particularly in studies with higher rates of DES use.

### Prevention of Bleeding in Patients Receiving Maintenance Triple Therapy

For patients receiving triple therapy, the dose of ASA should be kept as low as possible (i.e., 75 to 81 mg). Clopidogrel should be given at its standard dose of 75



mg/day, and warfarin should be administered under tight control to achieve a slightly lower target INR of 2.0 to 2.5. There is growing international experience with “low-dose” warfarin (INR 1.5 to 2.0) after low-profile, high-flow mechanical valve prostheses in the aortic valve position, particularly in the context of normal ventricular function; thromboembolic events are infrequently observed in these patients. The prophylactic administration of proton-pump inhibitors should be considered (10). Although recent data have identified a specific interaction with omeprazole, which might decrease platelet inhibition by clopidogrel (61), the clinical significance of this interaction will be determined by an ongoing randomized, controlled clinical trial. Finally, if bleeding events occur or if GI bleeding risk is high, ASA may be discontinued. In this context, the change in antiplatelet regimen most often linked to stent thrombosis or to the occurrence of death or MI after stent deployment has been discontinuation of the thienopyridine component of dual therapy (62–65).

### Patients Taking Warfarin and Undergoing Evaluation for PCI

Drug-eluting stents have been shown to be associated with a reduced need for target lesion revascularization in an increasing number of angiographic patient subsets and are now the predominant percutaneous revascularization strategy used in the U.S. Current guidelines recommend dual antiplatelet therapy for 1 year after DES. Therefore, the choices faced by the clinician caring for such patients are difficult. The operator implanting stents in patients who have a long-term need for warfarin should weigh the potential bleeding risk against the risk and consequences of restenosis in the stented site. In many cases, this balance might lead the operator to choose a BMS and commit the patient to a short course of clopidogrel (4 to 6 weeks) in addition to ASA and warfarin, rather than to an extended course of triple therapy. Given the risk of bleeding associated with triple therapy, BMS should be considered for use in target vessels less likely to benefit from DES (e.g., vessels >3 mm in diameter, short lesions <15 mm, and de novo stenoses). After deployment of BMS, duration of dual therapy may be shortened considerably. Although regimens as short as 2 to 4 weeks have been reported to offer adequate protection from early stent thrombosis with BMS, current guidelines recommend approximately 3 to 6 months of triple therapy, after which patients may continue on ASA and warfarin alone. Again, low-dose ASA (<100 mg) should be considered to decrease bleeding risk.

One alternative for such patients is to place a DES for treatment of very high-risk lesions and accept the small-

to-moderate but definite increase in risk of bleeding. If this strategy is chosen, warfarin should be administered with frequent monitoring so that the INR remains as close to 2.0 to 2.5 as possible, and low-dose ASA (<100 mg) should be given in combination with clopidogrel (75 mg). Moreover, in patients with high bleeding risk treated with DES for labeled indications, triple therapy may be limited to 3 to 6 months, with warfarin plus single antiplatelet therapy and a prophylactic proton-pump inhibitor continued thereafter (10).

The single antiplatelet agent most effective in preventing stent thrombosis and in reducing death or MI after coronary stent thrombosis seems to be clopidogrel (39,57,62–65). Wide interindividual variability in responsiveness to clopidogrel has been demonstrated with 15% to 31% (average 1 in 4) of patients being resistant to its effects on the basis of platelet function testing (66,67). Recent data demonstrate that insufficient clopidogrel active metabolite generation is the primary explanation for clopidogrel response variability and resistance (68,69). Variable levels of active metabolite generation associated with clopidogrel administration can be due to limited intestinal absorption, which is determined by efflux transported p-glycoprotein function that is affected by polymorphisms of the ABCB1 gene or functional variability in cytochrome P-450 isoenzyme activity due to drug–drug interactions and/or genetic polymorphisms of CYP450 isoenzymes (70,71). In this regard, the interaction of lipophilic statins, rifampin, St. John’s Wort, and calcium-channel blockers with CYP3A4 (72–74); selected proton pump inhibitors with CYP2C19 (61); and smoking with CYP1A2 (75) have all been reported to affect response to clopidogrel. Indeed, the CYP2C19 drug–drug interaction has been the putative explanation for attenuated clinical efficacy of clopidogrel treatment observed during concomitant administration of selected proton pump inhibitors, specifically omeprazole but not pantoprazole or esomeprazole (61,76). Recent studies have demonstrated an important relationship between the relatively common presence of a reduced function CYP2C19 allele, impaired platelet inhibition, and increased cardiovascular risk (71,77). These studies suggest that genetic testing might be an attractive future option used for personalizing antiplatelet therapy to optimize clinical outcomes. Furthermore, a recent study suggests that the addition of genetic information to clinical variables to create a pharmacogenetic algorithm to guide oral warfarin therapy provided a more accurate estimate of appropriate warfarin dose recommendations than could be obtained by either clinical variables alone or a fixed-dose approach (78). Hopefully, pharmacogenetic algorithms will enhance the safety and efficacy of triple therapy regimens in the future.

## Bleeding in Patients Receiving Triple Therapy

Bleeding that occurs while patients are receiving triple therapy is a particularly important problem. Management decisions are complex and might involve considerations of patient acuity as well as the site and severity of bleeding. Severe or life-threatening bleeding usually requires reversal of warfarin therapy. In rare instances, platelet transfusions might be needed to counteract concomitant thienopyridine therapy. If dual antiplatelet therapy requires urgent discontinuation, the patient should be closely monitored, particularly in the context of DES with their attendant risk of stent thrombosis. Table 3 compares outcomes in patients receiving triple versus dual antiplatelet therapy plus oral anticoagulation who underwent PCI (53,57,59,79–81).

In patients with mild or moderate bleeding, every effort should be made to maintain the INR as close to 2.0 as possible. In addition, ASA dose should be kept at <100 mg. If bleeding persists and anticoagulation is required (for instance, in patients with prosthetic heart valves, particularly in the mitral position), there is limited information with which to guide therapy. The concern in this setting remains the potential for valve or stent thrombosis. In particular, once bleeding is observed patients and practitioners might be tempted to stop all antiplatelet medications in addition to discontinuing warfarin. In a registry series (57), stent thrombosis was observed in 15.1% of patients treated with warfarin and ASA, whereas there were no occurrences of stent thrombosis in patients receiving warfarin and clopidogrel. Whether this difference represents the play of chance or reflects the relative importance of clopidogrel versus ASA in reducing stent thrombosis is unknown. Finally, strategies for reversing warfarin anticoagulation and employing interim anticoagulation with either unfraction-

ated or low-molecular-weight heparin are largely untried and unstandardized. Interim heparin anticoagulation might be used to “bridge” patients after acute treatment of the bleeding event and subsequent resumption of warfarin therapy.

## Changing Paradigms

Uncertainties surrounding the optimal strategy for combining ASA, clopidogrel, and warfarin in patients treated with DES who have an absolute indication for warfarin therapy will be further compounded by iterative changes in both antiplatelet and anticoagulation regimens that are likely to occur soon. Novel anticoagulant and antiplatelet regimens with more powerful antithrombotic potential are on the immediate horizon, as are stent designs that might prove less thrombogenic than current platforms, thus allowing briefer durations of thienopyridine therapy.

## Changes in Anticoagulant Drugs

Because of difficulties inherent in warfarin monitoring, such as variations in dose response and multiple drug-drug interactions, some have sought to replace warfarin with newer compounds that do not depend on vitamin K antagonism. The direct-acting oral thrombin antagonist ximelegatran was studied in patients with AF but was abandoned because of concerns regarding serious liver toxicity. Currently, a different direct antithrombin agent (dabigatran) is being evaluated in a similar patient population, but how this novel compound will interact with concomitant ASA and thienopyridine therapy is unknown.

Attention has also focused on antagonists of activated factor Xa as potential anticoagulants. The pro-thrombinase complex comprising Xa, FVa, calcium, and a negatively

Table 3

### Follow-Up Clinical Results in Studies Comparing Triple Therapy Versus Dual Antiplatelet Therapy in Patients Requiring Oral Anticoagulation and Undergoing Percutaneous Coronary Intervention

Author (Ref. #)	Outcome With Triple Therapy (vs. Dual Antiplatelet Therapy)			
	Absolute Reduction of Myocardial Infarction	Absolute Reduction of Stroke	Absolute Reduction of Stent Thrombosis	Absolute Increase of Major Bleeding
Khurram et al. (53)	NA	NA	NA	6.6%
DeEugenio et al. (79)	NA	NA	NA	11%*
Karjalainen et al. (57)	–2.6%	6.0%	4.0%	–5.2%
Ruiz-Nodar et al. (59)	3.9%	5.2%*†	0.1%	5.9%
Sarafoff et al. (80)	–1.2%	2.8%	1.2%	–1.7%
Rossini et al. (81)	0%	1%	1%	0.9%

\*p < 0.05; †Stroke + any thromboembolism.

charged phospholipid surface plays a crucial role in regulating the cleavage of prothrombin to thrombin (the “propagation phase” of thrombosis). Inhibition of Xa theoretically could control otherwise explosive thrombin generation, while still allowing upstream generation of minute quantities of thrombin to provide some margin of control over hemostasis.

The Xa antagonist idraparinux, which can be administered subcutaneously on a weekly schedule, was found to be noninferior to warfarin for prevention of thromboembolic events in patients with nonvalvular AF but was associated with an increase in serious bleeding, including intracranial hemorrhage (82). This trial also discouraged enrollment of patients who required antiplatelet therapy.

A variety of oral Xa antagonists currently being evaluated in clinical trials of patients with both AF and ACS offer greater insight into the safety of triple therapy regimens that incorporate ASA, clopidogrel, and an Xa antagonist. In a recent study of the oral Xa antagonist rivaroxaban, 3,491 subjects with ACS were stratified according to whether they received concomitant ASA alone or ASA and clopidogrel. Among subjects receiving concomitant ASA only, rivaroxaban therapy was associated with a modest increase in bleeding. Among subjects receiving the combination of ASA and clopidogrel, however, the composite bleeding rate increased from 3.5% in the placebo group to approximately 15% among those receiving the highest dose of rivaroxaban and 6% at the lowest dose (83). Similarly, in a smaller preliminary study of the Xa antagonist apixaban administered to patients with ACS, there was an apixaban dose-dependent increase in bleeding observed among patients receiving concomitant ASA and clopidogrel, ranging from 3% (placebo) to 7% (low-dose apixaban) to 9% (high-dose apixaban). This gradient of bleeding events was much less steep among patients receiving concomitant ASA alone (84). Thus, although these novel agents might eventually replace warfarin, available data suggest that when they are administered in combination with antiplatelet therapies, bleeding risk will be increased.

### Changes in Antiplatelet Drugs and Regimens

It is also likely that our armamentarium of antiplatelet drugs will change in the near future. Cloning of the target receptor for clopidogrel and elucidation of the metabolic pathways that activate it have led to the design of “third-generation” thienopyridines as well as nonthienopyridine P2Y<sub>12</sub> receptor antagonists. These new agents act more rapidly than clopidogrel and achieve a more profound blockade of the receptor.

One such third-generation thienopyridine is prasugrel, which is converted to its active metabolite more efficiently than clopidogrel and provides more rapid and intense levels of P2Y<sub>12</sub> blockade (85). Prasugrel was evaluated in the pivotal TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38) study, in which patients with ACS and planned PCI were randomly assigned to treatment with either prasugrel (60-mg oral load, 10 mg/day) or clopidogrel (300-mg oral load, 75 mg/day). At a median follow-up of 14 months, prasugrel was associated with a 19% reduction in the trial composite ischemic end point (cardiovascular death, MI, or stroke) and a nearly 52% reduction in stent thrombosis; however, an increased risk of major or fatal bleeding was also observed. A post hoc analysis revealed that most bleeding occurred in patients with advanced age ( $\geq 75$  years), low body weight ( $< 60$  kg), or prior manifestations of cerebrovascular disease (transient ischemic attack or stroke) (86). Although prasugrel has not yet been approved by the U.S. Food and Drug Administration, it is likely to eventually find use in patients with high-risk ACS and possibly after complex stent placement. Although prasugrel has not been studied in combination with oral anticoagulants, the higher bleeding rate observed in combination with ASA (as compared with clopidogrel) makes it likely that adding warfarin will incur an incremental risk for bleeding. A shorter-acting, reversible P2Y<sub>12</sub> antagonist (AZD 6140) is currently being evaluated in clinical trials. Like prasugrel, its antiplatelet effect is more rapid and more potent than that of clopidogrel, but unlike either agent, direct-acting AZD 6140 does not require metabolic conversion (87) and has a shorter half-life (88), which might be advantageous when used in patients who also require warfarin.

Another class of antiplatelet drugs currently in development are the antagonists of the primary human thrombin receptor, protease activated receptor (PAR)-1. This receptor was sequenced and cloned in the early 1990s (89), and antagonists have been developed to block thrombin’s platelet-activating effects. The SCH 530348 is an orally administered PAR-1 antagonist that has been evaluated in phase II testing in patients with ACS who are undergoing coronary angiography with planned PCI (90). In the pilot study, therapy with SCH 530348 (vs. placebo) was initiated in conjunction with ASA and clopidogrel before angiography and continued for 60 days. Compared with placebo, there was no difference in incidence of bleeding, but a reduction in the composite end point of ischemic events was observed. Particularly encouraging was the apparent lack of excess bleeding in patients undergoing bypass surgery. Although SCH 530348 is being tested in larger phase III



trials, patients treated with warfarin have been excluded from enrollment.

If SCH 530348 becomes clinically available, however, and does not increase bleeding risk, physicians could be faced with the proposition of triple rather than dual antiplatelet therapy. Although it is difficult to predict the degree (if any) of warfarin interaction with triple antiplatelet therapy, it seems intuitive that the risk of bleeding during long-term “quadruple” therapy will likely be heightened. Conversely, if SCH 530348 proves effective and is associated with less bleeding, it could conceivably replace clopidogrel among patients who require warfarin and in whom ASA is continued—a modified triple combination that could prove safer than the combination of clopidogrel, ASA, and warfarin. Finally, use of alternative antiplatelet agents, such as the cyclo-oxygenase inhibitor triflusal—which is potentially associated with lower bleeding risk and has been demonstrated as safe and effective in combination with warfarin in patients with AF (91)—could prove useful in patients requiring oral anticoagulation and undergoing PCI; however, specific prospective, randomized studies are needed.

### Changes in Stent Design and Technology

New drugs cannot be considered in isolation from evolving stent technology. The currently available data regarding triple therapy after DES were gathered in patients treated with first-generation paclitaxel- and sirolimus-eluting stents. Second-generation stents, including zotarolimus- or everolimus-eluting platforms, have thinner struts and polymer coatings. Histopathologic studies in animals suggest that endothelial coverage of struts might be more complete in vessels treated with these stents, which also seem to be associated with less vascular inflammation (92). Consequently, these stents could be less subject to late thrombosis (vs. first-generation DES) and might require shorter durations of dual antiplatelet therapy.

The next generation of DES will also likely employ bioabsorbable polymers (93) that physiologically degrade over a period of months after drug elution; furthermore, fully bioabsorbable stent platforms are being evaluated in clinical trials and might become available (94). The requisite duration of dual antiplatelet therapy might be shorter when such bioresorbable devices are used. Similarly, stents designed to capture circulating endothelial precursor cells (CD34 receptor-positive endothelial progenitor cells) might promote vascular healing and undergo more rapid re-endothelialization, thus allowing shorter durations of dual antiplatelet therapy (95,96). The first generation of such “pro-healing” stents has undergone preliminary clinical trials with follow-up through 2 years (97,98).

## Conclusions

The combined use of antiplatelet and anticoagulant drugs for the treatment and prevention of complications of 2 or more coexisting conditions, such as AF, mechanical valve prosthesis, and/or a DES, is associated with an increase in bleeding complications that might range from mild or moderate to severe or life-threatening. This risk increases with the duration of therapy, which should therefore be limited to the time necessary for stent endothelialization in patients at high risk for bleeding events. Before committing a patient to triple therapy for an indefinite period, the physician should carefully consider approaches that might not require prolonged dual antiplatelet therapy in conjunction with warfarin. For patients who require triple therapy, careful follow-up is indicated, with low-dose (<100 mg) ASA, conventional dose (75 mg) clopidogrel, a lower target INR (approximately 2.0), and consideration of prophylactic proton-pump inhibition.

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## REFERENCES

1. Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease. *Chest* 2008;133:7765–8145.
2. Antithrombotic Trialists' Collaboration Collaborative. Meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324: 71–86.
3. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2008;51: 210–47.
4. King SB III, Smith SC Jr., Hirshfeld JW, et al. Focused update of the ACC/AHA/SCAI 2005 guidelines update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (2007 Writing Group to Review New Evidence and Update the 2005 ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2008;51:172–209.
5. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary intervention. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;26:804–47.
6. Kong DF, Hasselbad V, Kandzari DE, Newby LK, Califf RM. Seeking the optimal aspirin dose in acute coronary syndromes. *Am J Cardiol* 2002;90:622–5.
7. Aronow HD, Califf RM, Harrington RA, et al. Relation between aspirin dose, all cause mortality and bleeding in patients with recent cerebrovascular or coronary ischemic events. *Am J Cardiol* 2008; 102:1285–90.
8. Kelly JP, Kaufman DW, Jurgelson JM, et al. Risk of aspirin associated major upper gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413–6.
9. McQuaid KR, Laine L. Systematic review and meta analysis of adverse events of low dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006;119:624–38.



10. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2008;52:1502–17.
11. Topol EJ, Easton D, Harrington RA, et al. Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist tirofiban in coronary and cerebrovascular disease. *Circulation* 2003;108:399–406.
12. Jolly SS, Pogue J, Haladyn K, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: insights from the PCI-CURE study. *Eur Heart J* 2009;30:900–7.
13. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682–7.
14. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndrome. *N Engl J Med* 2007;357:2001–15.
15. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 2007;50:e1–157.
16. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2005;111:2099–106.
17. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
18. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527–33.
19. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention (CREDO trial). *JAMA* 2002;288:2411–20.
20. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706–17.
21. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005;95:1218–22.
22. Berger JS, Stevins A, Granger CB, ET al. Initial aspirin dose and outcome among ST-elevation myocardial infarction patients treated with fibrinolytic therapy. *Circulation* 2008;117:192–9.
23. Grines CL, Bonow RO, Casey DE, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary stents. *J Am Coll Cardiol* 2007;49:734–9.
24. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;334:1084–9.
25. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation* 1998;98:1597–603.
26. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998;339:1665–71.
27. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulant versus antiplatelet therapy after coronary stent implantation in high-risk patients: the multicenter aspirin and ticlopidine trial after coronary stenting (MATIS). *Circulation* 1998;98:2126–32.
28. Hall P, Nakamura S, Maiello L, et al. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation* 1996;93:215–22.
29. Ho PM, Fihn SD, Wang L. Clopidogrel and long-term outcomes after stent implantation for acute coronary syndrome. *Am Heart J* 2007;154:846–51.
30. Bernardi V, Szarfer J, Summay G, et al. Long-term versus short-term clopidogrel therapy in patients undergoing coronary stenting (from the Randomized Argentine Clopidogrel Stent [RACS] trial). *Am J Cardiol* 2007;99:349–52.
31. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation* 2007;116:2391–8.
32. Windecker S, Meier B. Late coronary stent thrombosis. *Circulation* 2007;116:1952–65.
33. Holmes DR Jr., Kereiakes DJ, Laskey WK, et al. Thrombosis and drug-eluting stents. *J Am Coll Cardiol* 2007;50:109–18.
34. Mauri L, Hsieh W, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020–9.
35. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030–9.
36. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998–1008.
37. Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:989–97.
38. Williams DO, Abbott JD, Kip KE, et al. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: report of the DEScover registry. *Circulation* 2006;114:2154–62.
39. Pfisterer M, Brunner-LaRocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of the drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006;48:2584–91.
40. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;369:667–778.
41. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;323:147–52.
42. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet* 1994;343:499–503.
43. Hurlen M, Abdolnour M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969–74.
44. Brauwer MA, van den Bergh PJ, Aengevaeren WR, et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 trial. *Circulation* 2003;106:659–65.
45. Van Es RF, Jonker JJ, Verheugt FW, et al. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109–13.
46. Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;357:217–27.
47. Testa L, Zoccai GB, Porto I, et al. Adjusted indirect meta-analysis of aspirin plus warfarin at international normalized ratios 2 to 3 versus aspirin plus clopidogrel after acute coronary syndromes. *Am J Cardiol* 2007;99:1637–42.
48. Chen LY, Shen WS. Epidemiology of atrial fibrillation: a current perspective. *Heart Rhythm* 2007;4:S1–6.
49. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:854–906.

50. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007;115:2689-96.
51. Buresly K, Eisenberg MJ, Zhang X, Pilot L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005;165:784-9.
52. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J* 2004;147:463-7.
53. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol* 2006;18:162-4.
54. Mattichak SJ, Reed PS, Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction. *J Interv Cardiol* 2005;18:163-6.
55. Porter A, Konstantion Y, Iakobishvili Z, Shachar L, Battler A, Hasdai D. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2006;68:56-61.
56. Nguyen MC, Lim YL, Walton A, et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? *Eur Heart J* 2007;28:1717-22.
57. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J* 2007;28:726-32.
58. Rogacka R, Chieffo A, Michev I, et al. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. *J Am Coll Cardiol Intv* 2008;1:56-61.
59. Ruiz-Nodar J, Marin F, Antonio Hurtado J, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation. *J Am Coll Cardiol* 2008;51:818-25.
60. Sick PB, Schuler G, Hauptmann KE, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007;48:1490-5.
61. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256-60.
62. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.
63. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement. *Circulation* 2006;113:2803-9.
64. Brar SS, Kim J, Brar SK, et al. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. *J Am Coll Cardiol* 2008;51:2220-7.
65. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159-68.
66. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance and the effect of pretreatment platelet reactivity. *Circulation* 2003;107:2908-13.
67. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation* 2004;109:166-71.
68. Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol* 2008;51:1935-7.
69. Erlinge D, Varenhorst C, Braun OO, et al. Patients with poor responsiveness to thienopyridine treatment or with diabetes have lower levels of circulating active metabolite, but their platelets respond normally to active metabolite added ex vivo. *J Am Coll Cardiol* 2008;52:1978-80.
70. O'Donoghue M, Wiviott SD. Clopidogrel response variability and future therapies: clopidogrel: does one size fit all? *Circulation* 2006;114:e600-6.
71. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-75.
72. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol* 2005;45:1157-64.
73. Wilkenson GR. Drug metabolism and variability among patients in drug response. *New Engl J Med* 2005;352:2211-21.
74. Siller-Matula JM, Lang I, Christ G, Jilma B. Calcium-channel blockers reduce the antiplatelet effect of clopidogrel. *J Am Coll Cardiol* 2008;52:1557-63.
75. Bliden KP, Dichiera J, Lawal L, et al. The association of cigarette smoking with enhanced platelet inhibition by clopidogrel. *J Am Coll Cardiol* 2008;52:531-3.
76. Siller-Matula JM, Spiel AO, Lang IM, et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2008;157:148.e1-5.
77. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354-62.
78. The International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;360:753-64.
79. DeEugenio D, Kolman L, DeCaro M, et al. Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. *Pharmacotherapy* 2007;27:691-6.
80. Sarafoff N, Ndrepepa G, Mehilli J, et al. Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. *J Intern Med* 2008;264:472-80.
81. Rossini R, Musumeci G, Lettieri C, et al. Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. *Am J Cardiol* 2008;102:1618-23.
82. Amadeus Investigators, Bousser MG, Bouthier J, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008;371:315-21.
83. Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine in Subjects With Acute Coronary Syndromes—Thrombolysis In Myocardial Infarction 46 (ATLAS-TIMI 46—presented at AHA 2008). Available at: <http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1766>. Accessed November 14, 2008.
84. Apixaban for Prevention of Acute Ischemic and Safety Events (APPRaise). Available at: <http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1737>. Accessed November 14, 2008.
85. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis In Myocardial Infarction 44 trial. *Circulation* 2007;116:2923-32.
86. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
87. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006;27:1038-47.
88. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007;50:1844-51.
89. Vu T, Hung D, Wheaton V, Coughlin S. Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. *Cell* 1991;64:1057-68.
90. Chackalamannil S, Wang Y, Greenlee WJ, et al. Discovery of a novel, orally active himbacine-based thrombin receptor antagonist (SCH 530348) with potent antiplatelet activity. *J Med Chem* 2008;51:3061-4.

91. Pérez-Gómez F, Alegría E, Berjón J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004;44:1557–66.
92. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. *J Am Coll Cardiol* 2008;52:333–42.
93. Grube E. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation* 2004;109:2168–71.
94. Macaya C, Moreno R. Bioabsorbable drug-eluting stents: the future of coronary angioplasty? *Nat Clin Pract Cardiovasc Med* 2008;5:598–9.
95. Co M, Tay E, Lee CH, et al. Use of endothelial progenitor cell capture stent (Genous Bio-Engineered R Stent) during primary percutaneous coronary intervention in acute myocardial infarction: intermediate- to long-term clinical follow-up. *Am Heart J* 2008;155:128–32.
96. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. *J Am Coll Cardiol* 2005;45:1574–9.
97. Silber S, de Winter R, Grisold M, et al. Clinical outcome for the endothelial progenitor cells capturing genous stent: first results of the 1-year follow-up in 5000 patients (abstr). *Circulation* 2008;118:S1043.
98. Chong E, Shen L, Soon CY, et al. Two years clinical registry follow up of endothelial progenitor cell capture stent versus sirolimus-eluting bioabsorbable polymer-coated stent versus bare metal stents in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction (abstr). *Circulation* 2008;118:S1043.

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